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Systems for Particle  
Technology

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## COMMENTS TO DOCKET # 99D-1738

CDER requires Particle Size Analysis at different delay times of the spray (Formation, Intermediate, Dissipate). As a result of measuring Particle Size Distribution of nasal sprays at several of customer sites, the following issues were raised. I have also created a recommended method for accomplishing the 3 delayed measurements.

\*"Formation, Intermediate, and Dissipate" (F/I/D) can be defined in a myriad of ways.

Is it based on real time (Formation = xx milliseconds after actuation of spray bottle? Intermediate = xx milliseconds after Formation stage?)

Is it based on Optical Concentration / Obscuration (blockage of the laser beam by a large number of droplets)?

If based on Optical Concentration, at what Obscuration level does the spray event start? At what level does it end?

What is the period of time for each stage? 1 millisecond?  
10 milliseconds? 10% of the total spray duration time?

\*Obscuration defines blockage of the laser beam, but is not the most sensitive method to start the spray measurement. As the first few droplets pass the laser beam, they diffract light onto certain channels of the detector. This diffraction can be detected much earlier than 1-2% obscuration, as 1-2% obscuration requires thousands of particles. and is therefore a more reliable way of detecting the start of the spray.

\*How long should each F/I/D measurement last? With laser diffraction instruments, it is possible to make 2000+ measurements per second, creating a series of 0.5ms long "snapshots" of the spray event! The higher the speed, the less representative each slice becomes. Our observations are that most nasal sprays events last a total of 100ms.

\*The manufacturer's recommended obscuration values are not really relative, as the spray device's properties and actuation force determines the obscuration. As the instrument manufacturer, we have no control over the obscuration (as we would with dry powder or suspension measurements), so we have to live with what the spray device is delivering, be it high or low!

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\*It is of utmost importance that a reliable method of actuating the spray device is used, as the PSD is totally dependent on the spray device actuation force and location of the spray device relative to the laser. A means to guarantee consistent and reproducible alignment of the spray with the laser is required. Ideally the spray device actuation values should be documented in the software along with the results, and be included any reports.

#### **OUR RECOMMENDATION:**

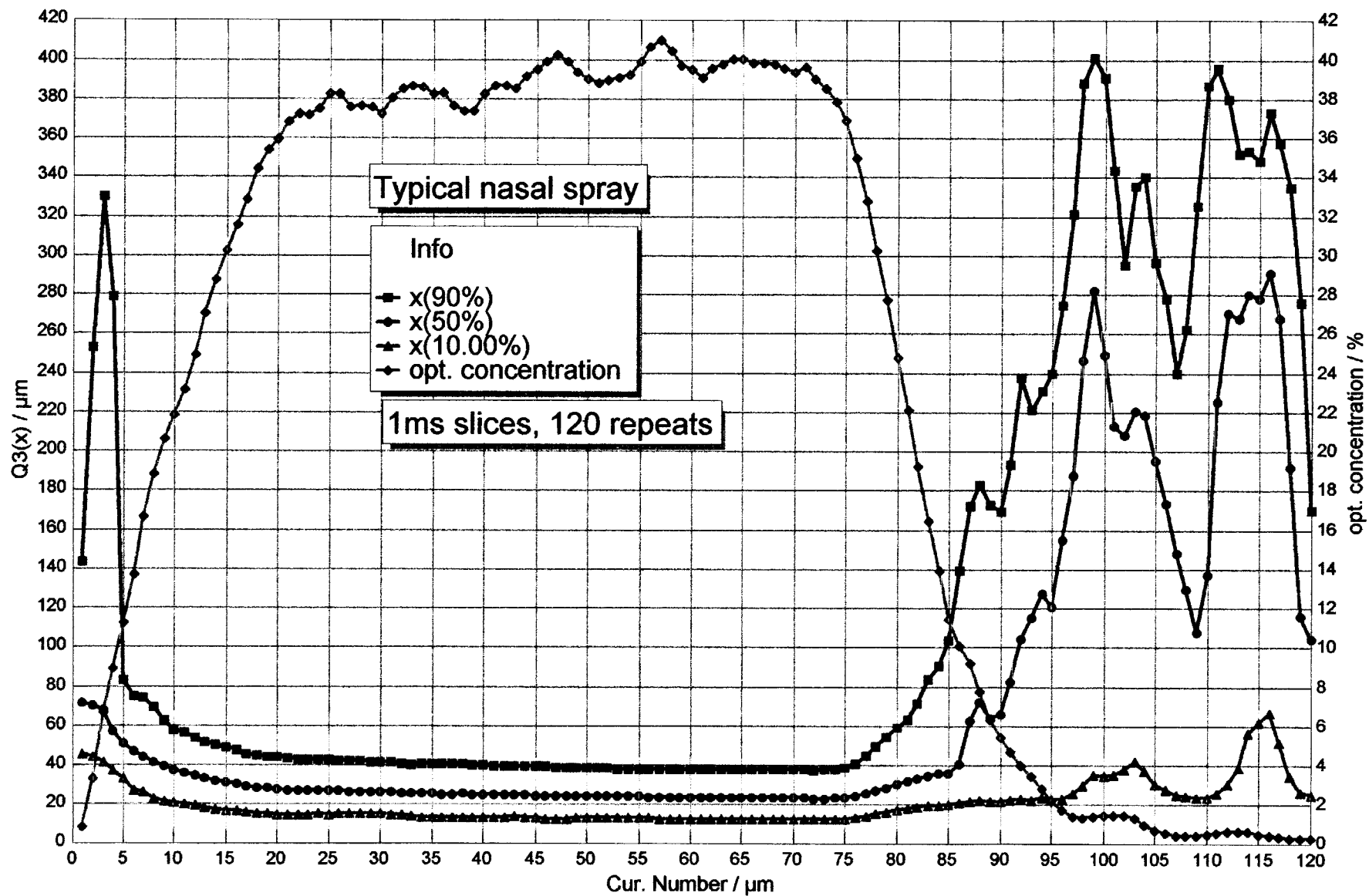
The measurement of the spray event should start when the signal on the most sensitive detector channel for the particular spray reaches 1%. This is a much more sensitive way to start the measurement, as it is based on detecting the passage of the first few droplets, compared to Obscuration or Optical Concentration where a mass of droplets are required. As the overall plume can best be characterized by obscuration, the **formation** measurement would begin when obscuration reaches 40% of the maximum obscuration value, and last 10ms. The **intermediate** measurement would begin when the obscuration reaches 98% of the maximum value, and last 10ms, and the **dissipation** measurement would begin when the obscuration decreases to 20% of the maximum value, and last 10ms. Time resolution should be 1ms or faster, with at least 100ms of data obtained per spray. A plot showing the entire spray event vs. time, with  $d_{10}/d_{50}/d_{90}$  and Optical Concentration, should be submitted, as well as the mean for F/I/D measurements.

Lastly, one measurement should be made which triggers at 1% signal on most sensitive channel, and continues uninterrupted until the signal falls below 1%, showing the average PSD for the entire spray dose.

Sincerely,

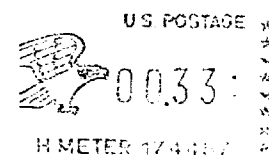
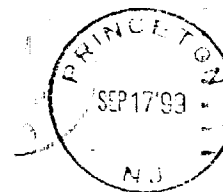
A handwritten signature in black ink, appearing to read "Joe Wolfgang".

Joe Wolfgang  
Sympatec Inc.





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